Perspective

Endoscopic ultrasonography: an advancing option with duality in both diagnosis and treatment of gastrointestinal oncology

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Abstract: Since their introduction into the clinical practices in 1980s, techniques of endoscopic ultrasonography (EUS) have been rapidly developing and are now in widespread use in gastrointestinal oncology. Evolving from the classical option, EUS today has been much innovated with addition of a variety of novel ideation which makes it a powerful tool with encouraging duality for both diagnostic and therapeutic purposes. There is a dire need for physicians in this field to understand the status quo of EUS as related to the management and detection of gastrointestinal tumors, which is globally reviewed in this paper.

Keywords: Gastrointestinal tract; oncology; ultrasonography; endoscopic; treatment

Submitted Oct 15, 2014. Accepted for publication Dec 02, 2014.
doi: 10.3978/j.issn.1000-9604.2014.12.14
View this article at: http://dx.doi.org/10.3978/j.issn.1000-9604.2014.12.14

Introduction

Since its introduction in the 1980s and, particularly beginning from this millennium, the rapidly developing endoscopic ultrasonography (EUS) has found its widespread use in clinical practice and played an important role in the diagnosis and treatment for tumors (1-5) in many disciplines, such as gastrointestinal oncology. Here we present a review on the advances of EUS in this field.

Endoscopic ultrasonography (EUS) as a diagnostic tool

EUS, a major diagnostic procedure for gastrointestinal submucosal tumors (SMTs) which not only clearly shows tumor location, size, margin, echo and originating layers (6) but also effectively identifies different tumors, is currently considered as the most accurate procedure for detecting and making diagnosis of SMTs for its high sensitivity and specificity (7-11).

EUS-guided fine needle aspiration biopsy (EUS-FNA) is a mature minimally invasive procedure in identifying and staging the diseases in the gastrointestinal tract and adjacent tissues or organs for its advantage in short puncture distance and good safety (12,13). EUS-FNA, though more often used in the biopsy of pancreas and lymph nodes, is also widely used in diagnosing various lesions including SMTs, applied in tissues and organs including intraperitoneal and mediastinal lymph nodes, pancreas, adrenal gland, gallbladder, bile ducts, liver, lung, kidney and rectum (14-16). It has been confirmed that EUS-FNA significantly improves the diagnostic accuracy with sensitivity of 80-85% and specificity of nearly 100% (17-19). According to recent studies, optical biopsy can be performed by penetrating a needle-like confocal laser endomicroscopic probe into pancreatic cystic lesions with puncture needle guided by EUS (20-23), which assists the evaluation of lesions but the sensitivity and accuracy is still to be confirmed by further study. Moreover, EUS-FNA is helpful in exploring the molecular pathogenesis of pancreatic cancer. EUS-FNA is used to obtain pancreatic tissues not only for molecular study and polymerase chain reaction (PCR) analysis, but also for DNA analysis to identify benign and malignant neoplasms, and for gene expression profile analysis in advanced pancreatic ductal adenocarcinoma (24-27). Suspected pancreatic ductal adenocarcinoma that cannot be determined by EUS-FNA may be subject to KRAS mutation analysis of the biopsy tissues (28,29). There are

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also studies on the diagnostic value of mucin (MUC1, MUC2 and MUC5AC) expression in biopsy tissues obtained from pancreas (30).

However, manipulation of EUS-FNA can be difficult and require skillful technique and the sensitivity and the negative predictive value of EUS-FNA for pancreatic tumor and other lesions is still insufficient. Meanwhile, as an invasive examination, EUS-FNA may cause complications including bleeding, infection and tumor rupture (31,32). In addition, some patients are not suitable candidates for EUS-FNA and/or unwilling to undergo EUS-FNA. Therefore, new techniques such as elastography, contrast-enhanced EUS (CE-EUS) are introduced clinically to improve the accuracy of EUS in differentiating the malignancy of lesions in recent years (33).

EUS elastography is a non-invasive procedure that has been used to evaluate the elasticity coefficient (firmness) and differentiate the malignancy of lesions besides obtain conventional ultrasound images (34). Giovannini *et al*. firstly reported the diagnostic value of EUS elastography in pancreatic masses and lymph nodes in 2006 (35) and proved that EUS elastography is superior to conventional EUS in its accuracy, sensitivity and specificity for differentiating the malignance of pancreatic masses and lymph nodes in a multi-center clinical study completed in 2009 (36). In an European multi-center study on computer-assisted quantitative analysis of continuous and dynamic EUS elastographic images carried out by Săftoiu *et al*., the accuracy, sensitivity, specificity, positive predictive value and negative predictive values of EUS elastography on the malignancy of space-occupying pancreatic lesions are 85.4%, 93.4%, 66.0%, 92.5% and 68.9%, respectively (37). The sensitivity and specificity of EUS elastography on lymph nodes are 91.1% and 60.0%, respectively, as reported by Sun *et al*. (38). Clinicians are often unable to specifically determine the nature of the lesions only based on EUS and elastographic images since the judgment is highly subjective and no consensus on the evaluation criteria has been reached yet in spite of the comparatively high accuracy of EUS elastography in identifying the malignancy of lesions. Nevertheless, EUS elastography is important in those unable to undergo EUS-FNA or the suspicious cases with repeated negative results in EUS-FNA. EUS elastography in identifying the malignancy of lymph nodes and pancreatic space-occupying lesion has been reported, still researches on its diagnostic value for other gastrointestinal space-occupying lesions are yet to be made (39). There might be more indications for EUS elastography after further study in the near future, including differentiating the malignancy of solid hepatic space-occupying lesions (40,41), assessing the invasion of esophageal and gastric cancer to adjacent organs and evaluating the solid adrenal lesions on the left by distinguishing adenomas from metastases (42).

CE-EUS (43), an imaging procedure that generates high resolution images of tissues in the body using ultrasound contrast agent, is now applied in the detection of solid tumors of the pancreas (cancers, neuroendocrine tumors), pancreatic cystic tumors (mucinous cystadenoma, intraductal papillary mucinous tumors), pancreatic pseudocyst, pancreatitis, and extrahepatic bile duct cancer (44,45), for identification of gastrointestinal stromal tumors, smooth muscle tumors (46) and adrenal tumors (47,48), and for differentiation of the malignancy of lymph nodes (49). Differences are noted in the enhancement mode, time-phase characteristics and classification of enhanced intensity between normal tissues and lesions. CE-EUS is demonstrated to be superior to multi-slice spiral CT for diagnosis of pancreatic mass of less than 2 cm and the diagnostic value of EUS-FNA is significantly improved when used in combination with CE-EUS (50).

EUS for therapeutic purposes

In recent years, studies on EUS in treatment for cancer are booming along with wide recognition of various emerging techniques. Interventional EUS therapy might not significantly improve the survival in malignant cases, but rather, it relieves pain, induces tumor cell necrosis and improves life quality.

EUS-guided celiac plexus neurolysis (EUS-CPN) is generally considered safe but it does not allow direct injection into celiac ganglia. According to Levy *et al*., 94% cancer patients achieved pain relief after EUS-guided celiac ganglia neurolysis (EUS-CGN), which initially implicates the safety of EUS-CGN and EUS-CPN (51). Ascunce *et al*. (52) and Sakamoto *et al*. (53) presented the safety and efficacy of EUS-CGN as well. Besides, Sakamoto *et al*. referred to EUS-guided broad plexus neurolysis (EUS-BPN) but did not give definite conclusion on its efficacy and safety. For EUS-CGN, no serious complications have been reported yet (54), however its efficacy and safety remains to be confirmed by in-depth research and large-sample clinical trials.

The development of interventional EUS techniques enables advanced pancreatic cancer patients undergo radioactive and chemotherapeutic seed implantation

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via EUS-guided fine-needle injection (EUS-FNI). Sun *et al*. firstly conducted EUS-guided iodine-125 seed implantation for pancreatic cancer in pig models in 2005 and no significant complications were noted (55), and then further clinical trials were performed in 2006 (56). Jin *et al*. (57) further evaluated the clinical efficacy and safety of EUS-guided iodine-125 radioactive seed implantation combined with gemcitabine for advanced pancreatic cancer. Nevertheless, studies on how to uniformly distribute seeds, the dosage control of radioactive seeds, and displacement of seeds after implantation are still to be made in EUS-guided radioactive seed implantation.

Image-guided radiation therapy (IGRT) guarantees for the accuracy and less complications of radiotherapy by real-time monitoring tumor or its markers by integrating radiation therapy machine with imaging equipment. In recent years, some scholars are trying to combine EUS techniques with IGRT along with the rapid development of EUS techniques. Park *et al*. treated advanced pancreatic cancer patients with IGRT by implanting gold fiducial markers with 19G needle guided by EUS and achieved a success rate of 88 % (58). In a retrospective study carried out by DiMaio *et al*., 30 cases with mediastinal and upper gastrointestinal cancer underwent EUS-guided IGRT, 97% of which achieved EUS-guided implantation of more flexible gold coil as reference marker using 22G needle without intraoperative complications (59). Both studies demonstrated the feasibility of EUS-guided gold fiducial placement for IGRT.

EUS-guided radiofrequency ablation (EUS-RFA) (60-62) and laser ablation (63) may shrink the tumor to some extent, but still clinical studies are to be performed to support its feasibility and safety.

EUS-guided biliary drainage has recently emerged as an effective procedure that utilizes EUS-guided puncture needle into the bile duct through gastric and duodenal wall, followed by insertion of guide wire along the needle, expansion and placement of drainage stent, thereby to establish internal drainage of biliary pathways to relieve bile duct obstruction. It is especially suitable for obstructive jaundice cases after failed ERCP regardless of its causes (64,65). Giovannini *et al*. (66) reported the first EUS-guided biliary and duodenal drainage in a patient with pancreatic cancer, and firstly performed EUS-guided hepaticogastrostomy (EUS-HGS) in a patient with proximal metastatic biliary obstruction in 2003 (67). Yamao *et al*. (68) reported cholecystoduodenostomy followed by biliary drainage in five cases, and they suggested that the procedure was more easily performed through duodenal bulb because of shorter puncture path into the extrahepatic bile duct, being free from vascular interference and puncture towards the hepatic portal; the drainage was carried out away from site of tumor obstruction; EUS-guided procedures were safer; and the dilated puncture channel enables large enough fistula to allow placement of 8.5 Fr bracket. In studies carried out by Artifon *et al*., there were no significant differences in the success rate, complications, cost of treatment and quality of life in malignant distal biliary obstruction patients who underwent EUS-guided choledochoduodenostomy and those who underwent percutaneous transhepatic biliary drainage (PTBD); for patients with distal bile duct cancer, no significant difference in technique and clinical outcomes was noted between the EUS-CD patient group and the surgery group, but there was only one case of self-limiting bleeding occurred in EUS-CD group and the cost of EUS-CD group was significantly lower than the surgery group (69). EUS-CD is a potentially effective non-surgical biliary drainage procedure in advanced malignant distal bile duct obstruction, in spite of the difficulties in operating EUS-CD and the lack of prospective and multi-center trials with large-sample size.

As the equipment and technique develop, EUS will offer much clearer images with more comprehensive functions, and it will be undoubtedly more and more applied in diagnosis and treatment of cancer with a promising future.

Acknowledgements

Funding: This study was sponsored by the Key Clinical Specialty Discipline Construction Program of Fujian, P.R.C and the Special Funds of Finance Department of Fujian Province (2012B013).
Disclosure: The author declares no conflict of interest.

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Cite this article as: Chen F. Endoscopic ultrasonography: an advancing option with duality in both diagnosis and treatment of gastrointestinal oncology. Chin J Cancer Res 2014;26(6):724-729. doi: 10.3978/j.issn.1000-9604.2014.12.14

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